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November 28, 2000

BOX PATENT APPLICATION
Assistant Commissioner for Patents
Washington, D.C. 20231

Re: Application of Claude COTREL, et al
OPTICALLY ACTIVE 5H-PYRROLO[3, 4-B]PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT
Our Ref: Q62017

Dear Sir:

This is a request for a Continuation Application of pending prior Application No. 09/124,651 filed July 29, 1998 of Claude COTREL and Gerard ROUSSEL, entitled OPTICALLY ACTIVE 5H-PYRROLO[3, 4-B]PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT.

This application is being filed under 37 C.F.R. § 1.53(b). Enclosed is a specification, including the claims, and a copy of the Declaration as filed in the prior application. Also enclosed is a copy of the REVOCATION AND APPOINTMENT OF ATTORNEYS as filed in Application No. 09/124,651, on November 28, 2000. The Assignment was also filed in Application No. 09/124,651, on November 28, 2000.

The prior application is assigned to Group Art Unit 1611.

Amend the specification by inserting before the first line the sentence:

--This is a continuation of Application No. 09/124,651, filed July 29, 1998, which is a continuation of 08/493,946, filed June 23, 1995 (abandoned), which is a continuation of 08/342,794, filed November 21, 1994 (abandoned), which is a continuation of 08/232,313, filed April 25, 1994 (abandoned), which is a continuation of 08/109,863, filed August 20, 1993 (abandoned), which is a continuation of 08/034,199, filed March 19, 1993 (abandoned), which is a continuation of 07/821,662, filed January 16, 1992 (abandoned), the disclosure of which is incorporated herein by reference.--

Priority is claimed from January 17, 1991, based on French Application No. 91 00490. The priority document was filed in parent Application No. 09/124,651.

A Preliminary Amendment is being submitted herewith.

The Government filing fee is calculated as follows:

Total claims	4 - 20	=		x	$18.00	= $.00
Independent claims	2 - 3	=		x	$80.00	= $.00
Base Fee						$710.00
TOTAL FILING FEE						**$710.00**

Attorney Docket No. Q62017
PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Claude COTREL, et al

Continuation of Appln. No.: 09/124,651 Group Art Unit: Not Yet Assigned

Filed: Concurrently Herewith Examiner: Not Yet Assigned

For: OPTICALLY ACTIVE 5H-PYRROLO[3, 4-B]PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT

EXCESS CLAIM FEE PAYMENT LETTER

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

An Amendment Under 37 C.F.R. § 1.111 is attached hereto for concurrent filing in the above-identified application. The resulting excess claim fee has been calculated as shown below:

	After Amendment		Highest No. Previously Paid For						
All Claims	64	-	20	=	44	X	$18.00	=	$792.00
Independent	14	-	3	=	11	X	$80.00	=	$880.00
					TOTAL			=	**$1672.00**

A check for the statutory fee of $1672.00 is attached. Please charge any additional fee or credit any overpayment to our Deposit Account No. 19-4880. A duplicate copy of this letter is enclosed.

Respectfully submitted,

Oliver R. Ashe, Jr.
Registration No. 40,491

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PATENT APPLICATION

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For: OPTICALLY ACTIVE 5H-PYRROLO[3, 4-B]PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Prior to examination, please amend the above-identified application as follows:

IN THE CLAIMS:

Cancel claims 1-4.

Add the following new claims:

5. A method of making a dextrorotatory isomer of zopiclone, 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, and pharmaceutically acceptable salts thereof, comprising the steps of:

a) forming a first reaction mixture by mixing a solution of an optically active acid in dichloromethane, to a solution of zopiclone in a first organic solvent;

b) concentrating the reaction mixture to dryness under reduced pressure to form a dry salt;

c) recrystallizing the salt in a second organic solvent to form a first crystallized product;

d) dissolving the crystallized product in a third organic solvent with reflux;

e) adding a fourth organic solvent to form a second reaction mixture;

f) maintaining the second reaction mixture to form a second crystallized product and recrystallizing the second crystallized product under the same conditions to obtain a crystallized salt;

g) dissolving the crystallized salt in water in the presence of a fifth organic solvent to form a third reaction mixture;

h) alkalizing the third reaction mixture to pH 11, collecting a first organic phase, extracting a remaining aqueous phase with a sixth organic solvent to obtain a second organic phase, collecting second organic phase, and recombining the first and second organic phases;

i) washing the recombined organic phases in water, then drying over magnesium sulfate, then filtering;

j) evaporating the solvent and recrystallizing the resulting product in a seventh organic solvent to obtain a dextrorotatory zopiclone isomer.

6. The method according to claim 5, wherein the first crystallized product has a melting temperature of 160-165°C and a rotatory power of $[\beta]^{20}_{D} = 83°$ (c = 0.5; acetone).

7. The method according to claim 5, wherein the second reaction mixture is maintained for 1 hour at 5°C.

8. The method according to claim 5, wherein the crystallized salt has a melting temperature of 160-165° C and a rotatory power of $[\beta]^{20}_{D} = 102°$ (c= 0.5; acetone).

9. The method according to claim 5, wherein the alkalizing of the third reaction mixture is achieved by the slow addition of a basic aqueous solution.

10. The method according to claim 5, wherein the dextrorotatory zopiclone isomer has a melting temperature of 206.5° C and a rotatory power of $[\beta]^{20}_{D} = 135° \pm 3°$ (c = 1.0; acetone).

11. The method according to claim 5, wherein the optically active acid is D(+)-O,O'-dibenzoyltartaric acid.

12. The method according to claim 5, wherein the first, third, fifth and sixth organic solvent is a halogenated aliphatic hydrocarbon.

13. The method according to claim 12, wherein the halogenated aliphatic hydrocarbon is dichloromethane, a nitrile, or combinations thereof.

14. The method according to claim 13, wherein the nitrile is acetonitrile.

15. The method according to claim 5, wherein the pharmaceutically acceptable salts are salts of mineral acids, or substitution derivatives thereof, selected from the group consisting of chlorohydrates, sulfates, nitrates, and phosphates.

16. The method according to claim 5, wherein the pharmaceutically acceptable salts are salts of organic acids, or substitution derivatives thereof, selected from the group consisting

of acetates, propionates, succinates, benzoates, fumarates, tartates, theophyllineacetates, salicylates, phenolphthalinates, and methylene-bis-β-oxynaphthoates.

17. A method of treatment of a dysfunction in the central nervous system of a human comprising administering to a human in need of such treatment, a therapeutically effective amount of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer.

18. The method according to claim 17, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered orally as a solid as a tablet, pill, powder or granule; orally as an emulsion, solution, suspension, syrup, or elixir; parenterally; or rectally.

19. The method according to claim 18, wherein the therapeutically effective amount administered is from about 2.5 mg to about 15 mg per day.

20. The method according to claim 17, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered together with a pharmaceutically acceptable carrier.

21. A method of induction of hypnosis in a human comprising administering to a human in need of such induction, a therapeutically effective amount of 6-(5-chloro-2-pyridyl)-5-

[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer.

22. The method according to claim 21, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered orally as a solid as a tablet, pill, powder or granule; orally as an emulsion, solution, suspension, syrup, or elixir; parenterally; or rectally.

23. The method according to claim 22, wherein the therapeutically effective amount administered is from about 2.5 mg to about 15 mg per day.

24. The method according to claim 21, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered together with a pharmaceutically acceptable carrier.

25. A method of sedation of a human comprising administering to a human in need of such sedation, a therapeutically effective amount of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer.

26. The method according to claim 25, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered

orally as a solid as a tablet, pill, powder or granule; orally as an emulsion, solution, suspension, syrup, or elixir; parenterally; or rectally.

27. The method according to claim 24, wherein the therapeutically effective amount administered is from about 2.5 mg to about 15 mg per day.

28. The method according to claim 25, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered together with a pharmaceutically acceptable carrier.

29. A method of relaxation of muscles in a human comprising administering to a human in need of relaxation, a therapeutically effective amount of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer.

30. The method according to claim 29, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory, is administered orally as a solid as a tablet, pill, powder or granule; orally as an emulsion, solution, suspension, syrup, or elixir; parenterally; or rectally.

31. The method according to claim 30, wherein the therapeutically effective amount administered is from about 2.5 mg to about 15 mg per day.

32. The method according to claim 29, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a

pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered together with a pharmaceutically acceptable carrier.

33. A method of tranquilization of a human comprising administering to a human in need of such tranquilization, a therapeutically effective amount of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer.

34. The method according to claim 33, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered orally as a solid as a tablet, pill, powder or granule; orally as an emulsion, solution, suspension, syrup, or elixir; parenterally; or rectally.

35. The method according to claim 34, wherein the therapeutically effective amount administered is from about 2.5 mg to about 15 mg per day.

36. The method according to claim 33, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered together with a pharmaceutically acceptable carrier.

37. A method of treatment of disorders that are affected by the binding of agonists to central nervous system benzodiazepine receptors in a human comprising administering to a human in need of such treatment, a therapeutically effective amount of 6-(5-chloro-2-pyridyl)-5-

[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer.

38. The method according to claim 37, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered orally as a solid as a tablet, pill, powder or granule; orally as an emulsion, solution, suspension, syrup, or elixir; parenterally; or rectally.

39. The method according to claim 38, wherein the therapeutically effective amount administered is from about 2.5 mg to about 15 mg per day.

40. The method according to claim 37, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered together with a pharmaceutically acceptable carrier.

41. A method of treatment of anxiety in a human comprising administering to a human in need of such treatment, a therapeutically effective amount of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer.

42. The method according to claim 41, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered

orally as a solid as a tablet, pill, powder or granule; orally as an emulsion, solution, suspension, syrup, or elixir; parenterally; or rectally.

43. The method according to claim 42, wherein the therapeutically effective amount administered is from about 2.5 mg to about 15 mg per day.

44. The method according to claim 41, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered together with a pharmaceutically acceptable carrier.

45. A method of increased duration of sleep in a human comprising administering to a human in need of such increased duration of sleep, a therapeutically effective amount of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer.

46. The method according to claim 45, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered orally as a solid as a tablet, pill, powder or granule; orally as an emulsion, solution, suspension, syrup, or elixir; parenterally; or rectally.

47. The method according to claim 46, wherein the therapeutically effective amount administered is from about 2.5 mg to about 15 mg per day.

48. The method according to claim 45, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered together with a pharmaceutically acceptable carrier.

49. A method of increased quality of sleep in a human comprising administering to a human in need of such increased quality of sleep, a therapeutically effective amount of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer.

50. The method according to claim 49, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered orally as a solid as a tablet, pill, powder or granule; orally as an emulsion, solution, suspension, syrup, or elixir; parenterally; or rectally.

51. The method according to claim 50, wherein the therapeutically effective amount administered is from about 2.5 mg to about 15 mg per day.

52. The method according to claim 49, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered together with a pharmaceutically acceptable carrier.

53. A method of reduction of the number of awakenings during sleep in a human comprising administering to a human in need of such reduction, a therapeutically effective amount of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer.

54. The method according to claim 53, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered orally as a solid as a tablet, pill, powder or granule; orally as an emulsion, solution, suspension, syrup, or elixir; parenterally; or rectally.

55. The method according to claim 54, wherein the therapeutically effective amount administered is from about 2.5 mg to about 15 mg per day.

56. The method according to claim 53, wherein 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, in the form of its dextrorotatory isomer, is administered together with a pharmaceutically acceptable carrier.

57. The dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, and pharmaceutically acceptable salts thereof.

58. The dextrorotatory isomer according to claim 57, wherein the pharmaceutically acceptable salts are salts of mineral acids, or substitution derivatives thereof, selected from the group consisting of chlorohydrates, sulfates, nitrates, and phosphates.

59. The dextrorotatory isomer according to claim 57, wherein the pharmaceutically acceptable salts are salts of organic acids, or substitution derivatives thereof, selected from the group consisting of acetates, propionates, succinates, benzoates, fumarates, tartates, theophyllineacetates, salicylates, phenolphthalinates, and methylene-bis-β-oxynaphthoates.

60. A composition comprising the dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof.

61. The composition according to claim 60, wherein the pharmaceutically acceptable salt is a salt of a mineral acid, or substitution derivatives thereof, selected from the group consisting of chlorohydrates, sulfates, nitrates, and phosphates.

62. The composition according to claim 60, wherein the pharmaceutically acceptable salt is a salt of an organic acid, or substitution derivatives thereof, selected from the group consisting of acetates, propionates, succinates, benzoates, fumarates, tartates, theophyllineacetates, salicylates, phenolphthalinates, and methylene-bis-β-oxynaphthoates.

63. A pharmaceutical composition comprising an effective amount of the dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

64. The pharmaceutical composition according to claim 63, wherein the pharmaceutically acceptable salt is a salt of a mineral acid, or substitution derivatives thereof, selected from the group consisting of chlorohydrates, sulfates, nitrates, and phosphates.

65. The pharmaceutical composition according to claim 63, wherein the pharmaceutically acceptable salt is a salt of an organic acid, or substitution derivatives thereof, selected from the group consisting of acetates, propionates, succinates, benzoates, fumarates, tartates, theophyllineacetates, salicylates, phenolphthalinates, and methylene-bis-β-oxynaphthoates.

66. The pharmaceutical composition according to claim 63, wherein the therapeutically effective amount of the dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo [3 ,4-b] pyrazine, or a pharmaceutically acceptable salt thereof, is from about 2.5 mg to about 15 mg.

67. The pharmaceutical composition according to claim 63, wherein the pharmaceutically acceptable carrier comprises a diluent, lubricant, sweetener, aromatic, or additive, or combinations thereof.

68. The pharmaceutical composition according to claim 67, wherein the additive is a wetting agent, emulsifier, dispersing agent, or combinations thereof.

REMARKS

Entry and consideration of this Amendment is respectfully requested.

Claims 5-16 are supported by the disclosure in Example 1 of the specification.

Claims 16, 61, 62, 64 and 65 are supported by the disclosure at page 4, line 20 to page 5, line 1 of the specification.

Claim 17 is supported by the disclosure at page 4, lines 2-4 of the specification.

Claims 18, 22, 26, 30, 34, 38, 42, 46, 50, and 54 are supported by the disclosure at page 5, line 2 to page 6, line 4 of the specification.

Claims 19, 23, 27, 31, 35, 39, 43, 47, 51, 55, and 66 are supported by the disclosure at page 6, lines 5-7 of the specification.

Claims 20, 24, 28, 32, 36, 40, 44, 48, 52, 56, 60 and 63 are supported by the disclosure in Example 2 of the specification.

Claim 21 is supported by the disclosure at page 4, lines 8-9 of the specification.

Claims 25 and 29 are supported by the disclosure at page 2, lines 14-16 and page 4, lines 5-7 of the specification.

Claim 33 is supported by the disclosure page 4, lines 5-7 of the specification.

Claim 41 is supported by the disclosure at page 2, lines 14-16 of the specification.

Claim 45, 49 and 53 are supported by the disclosure at page 4, lines 10-13 of the specification.

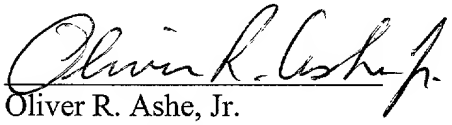
Claim 57 is supported by Example 1 of the specification.

Claims 58 and 59 are supported by the disclosure at page 4, lines 20-24 of the specification.

Claim 67 is supported by the disclosure at page 5, lines 2-8 of the specification.

Claim 68 is supported by the disclosure at page 4, lines 9-14 of the specification.

Respectfully submitted,



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Date: November 28, 2000

OPTICALLY ACTIVE 5H-PYRROLO[3,4-b]PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT

In French Patent FR 72/00,505, published under number 2,166,314, a description was given, in particular, of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, also known by the name of zopiclone, which is a noteworthy hypnotic product.

As a result of the presence of an asymmetric carbon atom at the 5-position of the 5H-pyrrolo[3,4-b]-pyrazine ring-system, zopiclone must be considered, in racemic form, to consist of a strictly equimolecular mixture of the laevorotatory and dextrorotatory forms.

It has now been found, and this forms the subject of the present invention, that the dextrorotatory isomer of zopiclone possesses properties which are not obvious in the light of those of racemic zopiclone.

The subject of the present invention is hence the dextrorotatory isomer of zopiclone, its preparation and pharmaceutical compositions containing it. In a racemic product, it is known that, often, one of the two enantiomers is active and that an enhancement of the toxicity may be linked to this activity, the other enantiomer being both markedly less active or inactive and less toxic. For such products, the gain in activity does

not compensate for the drawbacks due to an enhanced toxicity.

In the case of zopiclone, it was found, surprisingly and unexpectedly, not only that the dextrorotatory isomer is approximately twice as active as the racemate while having a lower toxicity than that of the racemate, but that the laevorotatory isomer is both almost inactive and more toxic than the racemate.

For example, when administered orally to mice, zopiclone possesses a toxicity (LD_50) in the region of 850 mg/kg, whereas the dextrorotatory isomer has a toxicity in the region of 1.5 g/kg and the laevorotatory isomer possesses an LD_50 of between 300 and 900 mg/kg.

In animals, the dextrorotatory isomer of zopiclone displays hypnotic, sedative, anxiolytic, muscle-relaxant and anticonvulsant properties.

From the standpoint of the potency of action in the main tests demonstrating the tranquillising and hypnotic activity of zopiclone, such as the test of affinity for central benzodiazepine receptor sites according to the technique of J.C. Blanchard and L. Julou, J. of Neurochemistry, 40, 601 (1983) based on the work of Squires and Braestrup, Nature, 266, 732-734 (1977), or the test of antagonist activity with respect to pentetrazol-induced convulsions according to the technique of Everett and Richards, J. Pharmacol., 81, 402 (1944), or in the writhing

reflex test in mice according to the technique of Zbinden and Randall, Advances in Pharmacology 5, 213-291 (1967), the dextrorotatory isomer is approximately twice as active whereas the laevorotatory isomer is almost inactive.

According to the invention, the dextrorotatory isomer of zopiclone may be prepared from the corresponding racemate according to the usual methods, such as chiral-phase chromatography, resolution of an optically active salt, stereoselective enzymatic catalysis by means of an appropriate microorganism, or asymmetric synthesis.

More especially, the dextrorotatory isomer of zopiclone may be obtained by resolution of zopiclone by means of an optically active acid, working in an appropriate organic solvent.

As an optically active acid which is especially suitable, D(+)-O,O'-dibenzoyltartaric acid may be mentioned.

Generally, the reaction is performed in an organic solvent chosen from halogenated aliphatic hydrocarbons such as dichloromethane and nitriles such as acetonitrile, taken alone or mixed.

By working in this manner, the salt of the dextrorotatory isomer precipitates and the laevorotatory isomer is extracted from the mother liquors of crystallisation.

The dextrorotatory isomer of zopiclone is displaced

from its salt by means of a base such as sodium hydroxide.

The dextrorotatory isomer of zopiclone is useful in humans for the treatment of states due to a dysfunction of the central nervous system.

The dextrorotatory isomer of zopiclone is, e.g., useful as a hypnosedative, tranquilliser, muscle relaxant and anticonvulsant.

However, the dextrorotatory isomer of zopiclone is more especially useful in man as a hypnotic.

Since it acts on the various parameters of sleep, the dextrorotatory isomer of zopiclone increases sleeptime and improves sleep quality, and decreases the number of episodes of waking at night and of early morning awakening.

The present invention relates to pharmaceutical compositions containing the dextrorotatory isomer of zopiclone or one of its pharmaceutically acceptable salts, in the pure state or in the presence of a diluent or a coating. These compositions may be employed orally, rectally or parenterally.

As pharmaceutically acceptable salts, salts of inorganic acids (such as hydrochlorides, sulphates, nitrates, phosphates) or organic acids (such as the acetates, propionates, succinates, benzoates, fumarates, tartrates, theophyllineacetates, salicylates, phenolphthalinates, methylenebis(β-hydroxynaphthoates), or of substitution derivatives of these acids, may be

mentioned.

As solid compositions for oral administration, tablets, pills, powders or granules may be used. In these compositions, the active product according to the invention is mixed with one or more inert diluents such as sucrose, lactose or starch. These compositions can also comprise substances other than diluents, e.g. a lubricant such as magnesium stearate.

As liquid compositions for oral administration, solutions, suspensions, syrups, elixirs and pharmaceutically acceptable emulsions, containing inert diluents such as water or liquid paraffin, may be used. These compositions can also comprise substances other than diluents, e.g. wetting, sweetening or flavouring products.

The compositions for parenteral administration can be suspensions, emulsions or aqueous or non-aqueous, sterile solutions. As a solvent or vehicle, propylene glycol, polyethylene glycol, vegetable oils, especially olive oil, and injectable organic esters, e.g. ethyl oleate, may be employed. These compositions can contain adjuvants, especially wetting, emulsifying and dispersing agents. The sterilisation may be carried out in several ways, e.g. using a bacteriological filter, by incorporating sterilising agents in the composition, by irradiation or by heating. They may be prepared in the form of sterile compositions which can be dissolved at the time of use in

sterile water or any other sterile injectable medium.

The compositions for rectal administration are suppositories which can contain, apart from the active product, excipients such as cocoa butter.

In human therapy, the doses depend on the effect sought and the treatment period; taken orally, they are generally between 2.5 and 15 mg per day for an adult.

The examples which follow, given without implied limitation, illustrate the present invention.

EXAMPLE 1

A solution of zopiclone (23.28 g; 0.06 mol) in dichloromethane (300 cc) is added to a solution of D(+)-O,O'-dibenzoyltartaric acid in the form of a monohydrate (22.56 g; 0.06 mol) in dichloromethane (300 cc). The reaction mixture is concentrated to dryness under reduced pressure. The crude salt obtained is recrystallised in acetonitrile (2000 cc) to give, in a 46 % yield, a crystallised product (21.3 g), m.p. 160-165°C (with decomposition), the optical rotation of which is $[\alpha]_D^{20} = 83°$ (c = 0.5; acetone).

The product obtained is dissolved in dichloromethane (180 cc) under reflux. Acetonitrile (200 cc) is added and the mixture is left standing for 1 hour at a temperature of 5°C. The crystallised product obtained is recrystallised again under the same conditions. A crystallised salt (16.5 g), m.p. 160-165°C (with

decomposition), the optical rotation of which is $[\alpha]_D^{20} = 102°$ (c = 0.5; acetone), is thereby obtained in a 36 % yield.

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalinised to pH 11 by slowly adding 2N aqueous sodium hydroxide solution. After settling has taken place, the aqueous phase is separated and extracted twice with dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration, evaporation of the solvent and recrystallisation of the product obtained in acetonitrile (80 cc), the dextrorotatory isomer (5.4 g) of zopiclone, m.p. 206.5°C, the optical rotation of which is $[\alpha]_D^{20} = 135° \pm 3°$ (c = 1.0; acetone), is obtained in a 23 % yield.

The mother liquors of crystallisation of the salt of zopiclone with D(+)-O,O'-dibenzoyltartaric acid are concentrated to dryness under reduced pressure to give a salt (22.05 g) the optical rotation of which is $[\alpha]_D^{20} = -21°$ (c = 0.2; acetone).

The salt thereby obtained is dissolved in water (125 cc) in the presence of dichloromethane (125 cc). The mixture is alkalinised to pH 11 by slowly adding 2N aqueous sodium hydroxide solution. After settling has taken place, the aqueous phase is separated and extracted twice with

dichloromethane. The combined organic phases are washed with water and then dried over magnesium sulphate. After filtration and evaporation of the solvent, the crystallised solid obtained (8.45 g) is recrystallised in acetonitrile (successively 100, 50 and 45 cc). The laevorotatory isomer (3.13 g) of zopiclone, m.p. 206.9°C, the optical rotation of which is $[\alpha]_D^{20} = -133° \pm 3°$ (c = 1.0; acetone), is thereby obtained in a 13.9 % yield.

EXAMPLE 2

Tablets containing 3 mg of active product and having the following composition are prepared according to the usual technique:

- dextrorotatory isomer of zopiclone.......	0.003 g
- starch...................................	0.100 g
- precipitated silica......................	0.035 g
- magnesium stearate.......................	0.005 g

CLAIMS

1. The dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyl-oxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, as well as its pharmaceutically acceptable salts.

2. A process for preparing the product according to claim 1, wherein racemic 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine is resolved by means of D(+)-O,O'-dibenzoyltartaric acid, working in an organic solvent, the salt of the dextrorotatory isomer is isolated and the dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)-carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]-pyrazine is displaced from its salt, then isolated and optionally converted to a pharmaceutically acceptable salt.

3. A pharmaceutical composition, which contains the product according to claim 1 in combination with one or more pharmaceutically acceptable diluents or adjuvants.

4. A method for improving sleep quality and time, wherein a sufficient quantity of the dextrorotatory isomer of zopiclone is administered to humans.

OPTICALLY ACTIVE 5H-PYRROLO[3,4-b]PYRAZINE DERIVATIVE, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT

RHONE-POULENC RORER S.A.

ABSTRACT

Dextrorotatory isomer of 6-(5-chloro-2-pyridyl)-5-[(4-methyl-1-piperazinyl)carbonyloxy]-7-oxo-6,7-dihydro-5H-pyrrolo[3,4-b]pyrazine, its preparation and pharmaceutical compositions containing it which are usable as tranquillisers and hypnotics.

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COMBINED DECLARATION AND POWER OF ATTORNEY FOR
ORIGINAL, DESIGN, NATIONAL STAGE OF PCT, SUPPLEMENTAL,
DIVISIONAL, CONTINUATION OR CONTINUATION-IN-PART APPLICATION

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name,

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled:

OPTICALLY ACTIVE 5H-PYRROLO[3,4-b]PYRAZINE DERIVATIVE, ITS PREPARATION AND
the specification of which PHARMACEUTICAL COMPOSITIONS CONTAINING IT

a. [X] is attached hereto

b. [ ] was filed on _____ as application Serial No. _____ and was amended on _____. (if applicable).

PCT FILED APPLICATION ENTERING NATIONAL STAGE

c. [ ] was described and claimed in International Application No. _____ filed on _____ and as amended on _____. (if any).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to the examination of this application in accordance with Title 37, Code of Federal Regulations, § 1.56(a).

[ ] I hereby claim foreign priority benefits under Title 35, United States Code § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

[ ] The attached 35 U.S.C. § 119 claim for priority for the U.S. application(s) listed below forms a part of this declaration.

Country	Application Number	Date of filing (day, month, yr)	Date of issue (day, month, yr)	Priority Claimed
France	91 00490	17/01/91		[X] YES [ ] NO
				[ ] YES [ ] NO
				[ ] YES [ ] NO

PATENT

Docket No. _____

ADDITIONAL STATEMENTS FOR
DIVISIONAL, CONTINUATION OR CONTINUATION-IN-PART

I hereby claim the benefit under Title 35, United States Code § 120 of any United States application(s) listed below.

Application Serial No.	Filing Date	Status (patented, pending, abandoned)

Application Serial No.	Filing Date	Status (patented, pending, abandoned)

[ ] In this continuation-in-part application, insofar as the subject matter of any of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose material information as defined in Title 37, Code of Federal Regulations, § 1.56(a) which occurred between the filing date of the prior application and the national or PCT international filing date of this application.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

I hereby appoint the following attorneys and/or agents with full power of substitution and revocation, to prosecute this application, to receive the patent, and to transact all business in the Patent and Trademark Office connected therewith: Jerome G. Lee (Reg. No. 16,967), John D. Foley (Reg. No. 16,836), John A. Diaz (Reg. No. 19,550), Thomas P. Dowling (Reg. No. 19,221), John C. Vassil (Reg. No. 19,098), Warren H. Rotert (Reg. No. 19,659), Alfred P. Ewert (Reg. No. 19,887), David H. Pfeffer, P.C. (Reg. No. 19,825), Harry C. Marcus (Reg. No. 22,390), Robert E. Paulson (Reg. No. 21,046), Stephen R. Smith (Reg. No. 22,615), Kurt E. Richter (Reg. No. 24,052), J. Robert Dailey (Reg. No. 27,434), Eugene Moroz (Reg. No. 25,237), John F. Sweeney (Reg. No. 27,471), Arnold I. Rady (Reg. No. 26,601), Christopher A. Hughes (Reg. No. 26,914), William S. Feiler (Reg. No. 26,728), Joseph A. Calvaruso (Reg. No. 28,287), James W. Gould (Reg. No. 28,859), Richard C. Komson (Reg. No. 27,913), Israel Blum (Reg. No. 26,710), Bartholomew Verdirame (Reg. No. 28,483), Maria C. H. Lin (Reg. No. 29,323) and Joseph A. DeGirolamo (Reg. No. 28,595) of Morgan & Finnegan whose address is: 345 Park Avenue, New York, New York 10154.

[X] I hereby authorize the U.S. attorneys and/or agents named hereinabove to accept and follow instructions from FREDERICK F. CALVETTI as to any action to be taken in the U.S. Patent and Trademark Office regarding this application without direct communication between the U.S. attorneys and/or agents and me. In the event of a change in the person(s) from whom instructions may be taken I will so notify the U.S. attorneys and/or agents named hereinabove.

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[ ] ATTACHED IS ADDED PAGE TO COMBINED DECLARATION AND POWER OF ATTORNEY FOR SIGNATURE BY THIRD AND SUBSEQUENT INVENTORS FORM.

* Before signing this declaration, each person signing must:

1. Review the declaration and verify the correctness of all information therein; and

2. Review the specification and the claims, including any amendments made to the claims.

After the declaration is signed, the specification and claims are not to be altered.

To the inventor(s):

The following are cited in or pertinent to the declaration attached to the accompanying application: